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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DI NOLA BARON, LILIANA	

ART UNIT	PAPER NUMBER
1615	

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7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/889,203	Applicant(s) BROWN, TRACEY	
	Examiner Liliana Di Nola-Baron	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

1. The use of the trademark TAXOL has been noted on page 5 in this application. The trademark should be entirely capitalized wherever it appears.

Claim Objections

2. Claims 2-5 are objected to because of the following informalities: the trademark TAXOL should be entirely capitalized. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 8 recites the limitation "an effective amount of said agent" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim, since the claim is directed to a method for the reduction of gastrointestinal toxicity of a drug, not of an agent.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-7 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Falk et al. (WO 91/040058).

Falk et al. discloses injectable formulations comprising an anti-cancer agent or chemotherapeutic agent and hyaluronic acid for the treatment of a disease or condition (See p. 17, line 2 to p. 18, line 14).

With regard to claim 1 of the instant application, Applicant describes impermeability of the target cell or organism to the active compound as one of the cellular mechanisms believed to be involved in cellular drug resistance (See Specification, p. 1, line 16 to p. 2, line 14). Falk et al. provides a method comprising administering a composition containing an amount of hyaluronic acid sufficient to facilitate penetration of the active agent through the tissue (See p. 20, line 10 to p. 21, line 5), thus the method disclosed by the international publication reduces or overcomes drug cellular resistance, as claimed by Applicant. With respect to the limitation, that the composition of hyaluronan and the active agent is more effective than the agent alone, the method of treatment disclosed by Falk et al. enhances the life expectancy and quality of life even in patients not responding to the usual treatments (See p. 35, line 31 to p. 36, line 1). Specifically, the international publication discloses the case of a patient affected by a tumor having a zero response rate to chemotherapy, who showed disease regression by 50% upon

treatment with chemotherapeutic agents in hyaluronic acid (See Case VI, p. 40, line 2 to p. 42, line 36). Thus the international publication provides a method comprising administering a chemotherapeutic agent with hyaluronan, wherein said agent is more effective than when administered alone, as claimed by Applicant.

With regard to claim 2, Falk et al. includes methotrexate and 5-fluorouracil among the suitable chemotherapeutic agents used in the invention (See p. 26, lines 15-18).

Regarding claim 3, Falk et al. teaches that the drug is mixed with hyaluronic acid (See p. 26, line 38 to p. 27, line 13).

With respect to claims 4 and 5, the compositions provided in the method disclosed by Falk et al. would inherently be capable of binding to receptors on the resistant cell and entering a resistant cell via bulk endocytosis, as said compositions comprise hyaluronic acid and a chemotherapeutic agent, as claimed by Applicant. Furthermore, Falk et al. teaches that the hyaluronic acid enhances the anti-neoplastic activity and effect of drugs and improves targeting (See p. 24, lines 13-33).

Regarding claims 6 and 7, the method disclosed by Falk et al. enhances transport and penetration of the drug into the tissue to be treated, and specifically to a tumor (See p. 23, line 30 to p. 24, line 6), thus the international publication provides a method to reduce or overcome a drug-resistant cancer, as claimed by Applicant.

With regard to claim 9, Falk et al. discloses injectable formulations comprising an anti-cancer agent or chemotherapeutic agent and an amount of hyaluronic acid sufficient to facilitate the agent's penetration through the tissue at the site to be treated (See p. 17, line 2 to p. 18, line 14). Thus, the compositions disclosed by Falk et al. reduce or overcome drug cellular resistance, as claimed by Applicant. Furthermore, the feature intended use claimed by Applicant has no patentable weight in a composition claim. With respect to the molecular weight of the hyaluronan claimed by Applicant, Falk et al. includes a sodium hyaluronate having a molecular weight of less than 750,000 Daltons as suitable hyaluronan used in the compositions of the invention (See p. 31, line 18 to p. 32, line 24) and contemplates the use of hyaluronic acid having greater molecular weight (See p. 33, lines 29-31). Thus the international publication provides compositions comprising hyaluronan having a molecular weight greater than 700,000 Daltons, as claimed by Applicant. Regarding the cytotoxic effect of the composition as compared to the effect of the agent alone, the compositions disclosed by Falk et al. enhance the life expectancy and quality of life even in patients not responding to the usual treatments (See p. 35, line 31 to p. 36, line 1). Specifically, the patent discloses the case of a patient affected by a tumor having a zero response rate to chemotherapy, who showed disease regression by 50% upon treatment with chemotherapeutic agents in hyaluronic acid (See Case VI, p. 40, line 2 to p. 42, line 36). Thus the international publication provides a composition comprising a chemotherapeutic agent with hyaluronan, wherein said agent is more effective than when administered alone, as claimed by Applicant.

The methods and compositions disclosed by Falk et al. meet the limitations of claims 1-7 and 9 of the instant application, as the international publication contemplates a method of overcoming cellular drug resistance comprising co-administering an anti-neoplastic agent and hyaluronan, and compositions comprising an anti-neoplastic agent and hyaluronan. Thus, the international publication anticipates the claimed invention.

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

8. Claims 1-7 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Falk et al. (U.S. Patent 5,985,850).

Falk et al. discloses injectable formulations comprising an anti-cancer agent or chemotherapeutic agent and hyaluronic acid for the treatment of a disease or condition (See col. 10, lines 8-59).

With regard to claim 1 of the instant application, Applicant describes impermeability of the target cell or organism to the active compound as one of the cellular mechanisms believed to be involved in cellular drug resistance (See Specification, p. 1, line 16 to p. 2, line 14). Falk et al. provides a method comprising administering a composition containing an amount of hyaluronic acid sufficient to facilitate penetration of the active agent through the tissue (See col. 11, line 66 to col. 12, line 34), thus the method disclosed by the patent reduces or overcomes drug cellular resistance, as claimed by Applicant. With respect to the limitation, that the composition of hyaluronan and the active agent is more effective than the agent alone, the method of treatment disclosed by Falk et al. enhances the life expectancy and quality of life even in patients not responding to the usual treatments (See col. 20, lines 39-47). Specifically, the patent discloses the case of a patient affected by a tumor having a zero response rate to chemotherapy, who showed disease regression by 50% upon treatment with chemotherapeutic agents in hyaluronic acid (See Case VI, col. 22, line 65 to col. 24, line 28). Thus the patent provides a method comprising administering a chemotherapeutic agent with hyaluronan, wherein said agent is more effective than when administered alone, as claimed by Applicant.

With regard to claim 2, Falk et al. includes methotrexate and 5-fluorouracil among the suitable chemotherapeutic agents used in the invention (See col. 15, lines 35-38).

Regarding claim 3, Falk et al. teaches that the drug is mixed with hyaluronic acid (See col. 15, line 55 to col. 16, line 3).

With respect to claims 4 and 5, the compositions provided in the method disclosed by Falk et al. would inherently be capable of binding to receptors on the resistant cell and entering a resistant cell via bulk endocytosis, as said compositions comprise hyaluronic acid and a chemotherapeutic agent, as claimed by Applicant. Furthermore, Falk et al. teaches that the hyaluronic acid enhances the anti-neoplastic activity and effect of drugs and improves targeting (See col. 14, lines 22-42).

Regarding claims 6 and 7, the method disclosed by Falk et al. enhances transport and penetration of the drug into the tissue to be treated, and specifically to a tumor (See col. 14, lines 1-15), thus the patent provides a method to reduce or overcome a drug-resistant cancer, as claimed by Applicant.

With regard to claim 9, Falk et al. discloses injectable formulations comprising an anti-cancer agent or chemotherapeutic agent and an amount of hyaluronic acid sufficient to facilitate the agent's penetration through the tissue at the site to be treated (See col. 10, lines 8-59). Thus, the compositions disclosed by Falk et al. reduce or overcome drug cellular resistance, as claimed by Applicant. Furthermore, the feature intended use claimed by Applicant has no patentable weight in a composition claim. With respect to the molecular weight of the hyaluronan claimed by Applicant, Falk et al. includes a sodium hyaluronate having a molecular weight of less than 750,000 Daltons as suitable hyaluronan used in the compositions of the invention (See col. 18, lines 29-56) and contemplates the use of hyaluronic acid having greater molecular weight (See col. 19, lines 31-33). Thus the patent provides compositions comprising hyaluronan having a

molecular weight greater than 700,000 Daltons, as claimed by Applicant. Regarding the cytotoxic effect of the composition as compared to the effect of the agent alone, the compositions disclosed by Falk et al. enhance the life expectancy and quality of life even in patients not responding to the usual treatments (See col. 20, lines 39-47). Specifically, the patent discloses the case of a patient affected by a tumor having a zero response rate to chemotherapy, who showed disease regression by 50% upon treatment with chemotherapeutic agents in hyaluronic acid (See Case VI, col. 22, line 65 to col. 24, line 28). Thus the patent provides a composition comprising a chemotherapeutic agent with hyaluronan, wherein said agent is more effective than when administered alone, as claimed by Applicant.

The methods and compositions disclosed by Falk et al. meet the limitations of claims 1-7 and 9 of the instant application, as the patent contemplates a method of overcoming cellular drug resistance comprising co-administering an anti-neoplastic agent and hyaluronan, and compositions comprising an anti-neoplastic agent and hyaluronan. Thus, the patent anticipates the claimed invention.

9. Claims 1, 6, 7 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Turley et al. (U.S. Patent 6,475,795).

Turley et al. disclose pharmaceutical compositions comprising an anti-sense nucleic acid bound to hyaluronan for the treatment of a human suffering from a disease or condition treatable using gene therapy, including tumors (See col. 6, line 60 to col. 7, line 10, col.2, line 62 to col. 3, line 7 and claims 1-8), and provides methods of targeting gene therapy in a human comprising administering said compositions by systemic administration (See col. 4, line 10 to col. 5, line 13).

With regard to the method claimed in claim 1 of the instant application, in the specification Applicant includes impermeability of the target cell or organism to the active compound among the cellular mechanisms believed to be involved in cellular drug resistance (See p. 1, line 16 to p. 2, line 14). Turley et al. describes a method comprising administering hyaluronan bound a nucleotide to efficiently enhance the uptake of nucleotides into the cell and target them into the nucleus, while reducing the nucleotide concentration required for biological efficacy (See col. 12, lines 6-63). Thus, the method provided by Turley et al., which increases the uptake the antineoplastic agent into the cell and the nucleus and reduces the amount of drug required for biological activity, reduces or overcomes drug cellular resistance, as claimed by Applicant. With respect to the cytotoxic effect of the composition claimed by Applicant versus the antineoplastic agent alone, Turley et al. teaches that the addition of hyaluronan to the nucleotide composition reduces the concentration requirement of the active agent and increases the antineoplastic activity of the composition as compared to the agent alone (See col. 12, lines 34-43).

With respect to claims 6 and 7 of the instant application, Turley et al. provides a method to improve targeting gene therapy in a human for the treatment of a disease, by enhancing the uptake of nucleotides into the cell (See col. 12, lines 6-63), and includes cancer cells among the cells targeted by the compositions and method of the invention (See claims 1, 7 and 8).

Regarding claim 9, Turley et al. discloses pharmaceutical compositions comprising an anti-sense nucleic acid bound to hyaluronan for the treatment of a human suffering from a disease or condition treatable using gene therapy, including tumors (See col. 6, line 60 to col. 7, line 10, col.2, line 62 to col. 3, line 7 and claims 1-8), and provides forms of hyaluronan having molecular weights between 150,000 and 750,000 Daltons (See col. 7, lines 11-15). Additionally, Turley et al. contemplates the use of higher molecular weight hyaluronans (See col. 10, lines 6-9). Thus the patent contemplates pharmaceutical compositions comprising a hyaluronan having a molecular weight greater than 700,000 Daltons and an anti-neoplastic agent, as claimed by Applicant. These compositions would inherently reduce or overcome acquired or inherent cellular resistance. Furthermore, the feature intended use claimed by Applicant, i.e., the use of the composition to reduce or overcome cellular resistance, has no patentable weight in a composition claim.

With regard to the administration of said composition, Turley et al. includes intravenous administration and injection among the routes of administration suitable for the invention (See col. 4, line 65 to col. 5, line 13). Said routes are systemic forms of administration.

With respect to the effectiveness of the composition, Turley et al. teaches that the amount of the gene therapy agent used in the invention is reduced compared to the amount normally used in ordinary gene therapy treatment without hyaluronan, because of the enhanced transport by the hyaluronan (See col. 5, lines 21-25 and col. 12, lines 54-63).

The method and pharmaceutical compositions disclosed by Turley et al. meet the limitations of claims 1, 6, 7 and 9 of the instant application, as the patent contemplates a method for increasing the uptake of antineoplastic agents into human cells and compositions for systemic administration comprising an antineoplastic agent and hyaluronan having molecular weight greater than 700,000 Daltons and having increased uptake into the cells. Thus, the patent anticipates the claimed invention.

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 1-7 and 9 are rejected under 35 U.S.C. 102(a) as being anticipated by Falk et al. (U.S. Patent 5,985,850).

Falk et al. discloses injectable formulations comprising an anti-cancer agent or chemotherapeutic agent and hyaluronic acid for the treatment of a disease or condition (See col. 10, lines 8-59).

With regard to claim 1 of the instant application, Applicant describes impermeability of the target cell or organism to the active compound as one of the cellular mechanisms believed to be

involved in cellular drug resistance (See Specification, p. 1, line 16 to p. 2, line 14). Falk et al. provides a method comprising administering a composition containing an amount of hyaluronic acid sufficient to facilitate penetration of the active agent through the tissue (See col. 11, line 66 to col. 12, line 34), thus the method disclosed by the patent reduces or overcomes drug cellular resistance, as claimed by Applicant. With respect to the limitation, that the composition of hyaluronan and the active agent is more effective than the agent alone, the method of treatment disclosed by Falk et al. enhances the life expectancy and quality of life even in patients not responding to the usual treatments (See col. 20, lines 39-47). Specifically, the patent discloses the case of a patient affected by a tumor having a zero response rate to chemotherapy, who showed disease regression by 50% upon treatment with chemotherapeutic agents in hyaluronic acid (See Case VI, col. 22, line 65 to col. 24, line 28). Thus the patent provides a method comprising administering a chemotherapeutic agent with hyaluronan, wherein said agent is more effective than when administered alone, as claimed by Applicant.

With regard to claim 2, Falk et al. includes methotrexate and 5-fluorouracil among the suitable chemotherapeutic agents used in the invention (See col. 15, lines 35-38).

Regarding claim 3, Falk et al. teaches that the drug is mixed with hyaluronic acid (See col. 15, line 55 to col. 16, line 3).

With respect to claims 4 and 5, the compositions provided in the method disclosed by Falk et al. would inherently be capable of binding to receptors on the resistant cell and entering a resistant

cell via bulk endocytosis, as said compositions comprise hyaluronic acid and a chemotherapeutic agent, as claimed by Applicant. Furthermore, Falk et al. teaches that the hyaluronic acid enhances the anti-neoplastic activity and effect of drugs and improves targeting (See col. 14, lines 22-42).

Regarding claims 6 and 7, the method disclosed by Falk et al. enhances transport and penetration of the drug into the tissue to be treated, and specifically to a tumor (See col. 14, lines 1-15), thus the patent provides a method to reduce or overcome a drug-resistant cancer, as claimed by Applicant.

With regard to claim 9, Falk et al. discloses injectable formulations comprising an anti-cancer agent or chemotherapeutic agent and an amount of hyaluronic acid sufficient to facilitate the agent's penetration through the tissue at the site to be treated (See col. 10, lines 8-59). Thus, the compositions disclosed by Falk et al. reduce or overcome drug cellular resistance, as claimed by Applicant. Furthermore, the feature intended use claimed by Applicant has no patentable weight in a composition claim. With respect to the molecular weight of the hyaluronan claimed by Applicant, Falk et al. includes a sodium hyaluronate having a molecular weight of less than 750,000 Daltons as suitable hyaluronan used in the compositions of the invention (See col. 18, lines 29-56) and contemplates the use of hyaluronic acid having greater molecular weight (See col. 19, lines 31-33). Thus the patent provides compositions comprising hyaluronan having a molecular weight greater than 700,000 Daltons, as claimed by Applicant. Regarding the cytotoxic effect of the composition as compared to the effect of the agent alone, the compositions

disclosed by Falk et al. enhance the life expectancy and quality of life even in patients not responding to the usual treatments (See col. 20, lines 39-47). Specifically, the patent discloses the case of a patient affected by a tumor having a zero response rate to chemotherapy, who showed disease regression by 50% upon treatment with chemotherapeutic agents in hyaluronic acid (See Case VI, col. 22, line 65 to col. 24, line 28). Thus the patent provides a composition comprising a chemotherapeutic agent with hyaluronan, wherein said agent is more effective than when administered alone, as claimed by Applicant.

The methods and compositions disclosed by Falk et al. meet the limitations of claims 1-7 and 9 of the instant application, as the patent contemplates a method of overcoming cellular drug resistance comprising co-administering an anti-neoplastic agent and hyaluronan, and compositions comprising an anti-neoplastic agent and hyaluronan. Thus, the patent anticipates the claimed invention.

11. Claims 1, 6, 7 and 9 are rejected under 35 U.S.C. 102(a) as being anticipated by Turley et al. U.S. Patent 6,475,795).

Turley et al. disclose pharmaceutical compositions comprising an anti-sense nucleic acid bound to hyaluronan for the treatment of a human suffering from a disease or condition treatable using gene therapy, including tumors (See col. 6, line 60 to col. 7, line 10, col.2, line 62 to col. 3, line 7 and claims 1-8), and provides methods of targeting gene therapy in a human comprising

administering said compositions by systemic administration (See col. 4, line 10 to col. 5, line 13).

With regard to the method claimed in claim 1 of the instant application, in the specification Applicant includes impermeability of the target cell or organism to the active compound among the cellular mechanisms believed to be involved in cellular drug resistance (See p. 1, line 16 to p. 2, line 14). Turley et al. describes a method comprising administering hyaluronan bound a nucleotide to efficiently enhance the uptake of nucleotides into the cell and target them into the nucleus, while reducing the nucleotide concentration required for biological efficacy (See col. 12, lines 6-63). Thus, the method provided by Turley et al., which increases the uptake the antineoplastic agent into the cell and the nucleus and reduces the amount of drug required for biological activity, reduces or overcomes drug cellular resistance, as claimed by Applicant. With respect to the cytotoxic effect of the composition claimed by Applicant versus the antineoplastic agent alone, Turley et al. teaches that the addition of hyaluronan to the nucleotide composition reduces the concentration requirement of the active agent and increases the antineoplastic activity of the composition as compared to the agent alone (See col. 12, lines 34-43).

With respect to claims 6 and 7 of the instant application, Turley et al. provides a method to improve targeting gene therapy in a human for the treatment of a disease, by enhancing the uptake of nucleotides into the cell (See col. 12, lines 6-63), and includes cancer cells among the cells targeted by the compositions and method of the invention (See claims 1, 7 and 8).

Regarding claim 9, Turley et al. discloses pharmaceutical compositions comprising an anti-sense nucleic acid bound to hyaluronan for the treatment of a human suffering from a disease or condition treatable using gene therapy, including tumors (See col. 6, line 60 to col. 7, line 10, col.2, line 62 to col. 3, line 7 and claims 1-8), and provides forms of hyaluronan having molecular weights between 150,000 and 750,000 Daltons (See col. 7, lines 11-15). Additionally, Turley et al. contemplates the use of higher molecular weight hyaluronans (See col. 10, lines 6-9). Thus the patent contemplates pharmaceutical compositions comprising a hyaluronan having a molecular weight greater than 700,000 Daltons and an anti-neoplastic agent, as claimed by Applicant. These compositions would inherently reduce or overcome acquired or inherent cellular resistance. Furthermore, the feature intended use claimed by Applicant, i.e., the use of the composition to reduce or overcome cellular resistance, has no patentable weight in a composition claim.

With regard to the administration of said composition, Turley et al. includes intravenous administration and injection among the routes of administration suitable for the invention (See col. 4, line 65 to col. 5, line 13). Said routes are systemic forms of administration.

With respect to the effectiveness of the composition, Turley et al. teaches that the amount of the gene therapy agent used in the invention is reduced compared to the amount normally used in ordinary gene therapy treatment without hyaluronan, because of the enhanced transport by the hyaluronan (See col. 5, lines 21-25 and col. 12, lines 54-63).

The method and pharmaceutical compositions disclosed by Turley et al. meet the limitations of claims 1, 6, 7 and 9 of the instant application, as the patent contemplates a method for increasing the uptake of antineoplastic agents into human cells and compositions for systemic administration comprising an antineoplastic agent and hyaluronan having molecular weight greater than 700,000 Daltons and having increased uptake into the cells. Thus, the patent anticipates the claimed invention.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Falk et al. (U.S. Patent 5,985,850).

With respect to claim 8 of the instant application, the patent does not specifically teach that the method of the invention reduces gastrointestinal toxicity of a drug, however, the method of treatment provided by Falk et al. comprises administering as a mixture a non-toxic combination of an anti-cancer or chemotherapeutic agent and hyaluronic acid, wherein the composition has no adverse effects (See col. 10, line 60 to col. 11, line 32 and col. 15, lines 39-56). Furthermore, Falk et al. teaches that the combination and method of the invention enhance the expectancy and

quality of life even in those cancer patients not responding to the usual treatments and enable the body to eliminate toxins (See col. 20, lines 39-47). It is the view of the examiner that gastrointestinal toxicity is one of the most common side effects experienced by patients taking chemotherapeutic agents, such as methotrexate. As Falk et al. provides the general teachings that the compositions of the invention are non toxic, provide no adverse affect and help the body eliminate toxins, it would be expected that administration of said composition would reduce gastrointestinal toxicity as compared to the effect of compositions comprising the chemotherapeutic agent alone.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Falk et al. to device a method for reducing gastrointestinal toxicity of a drug, comprising systemically administering a composition comprising a mixture of the drug with hyaluronic acid. The expected result would have been a successful method for the administration of non-toxic anti-cancer agent compositions having reduced adverse effects. Because of the teachings of Falk et al., that compositions comprising an anti-cancer or chemotherapeutic agent and hyaluronic acid are non toxic and present no adverse effects, one of ordinary skill in the art would have a reasonable expectation that the method claimed in the instant application would be successful in reducing drug toxicity in the gastrointestinal tract of a patient. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liliana Di Nola-Baron whose telephone number is 703-308-8318. The examiner can normally be reached on Monday through Thursday, 5:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-1234/ 1235.

Liliana Di Nola Baron

October 13, 2003

Liliana Di Nola-Baron
Patent Examiner
Art Unit 1615